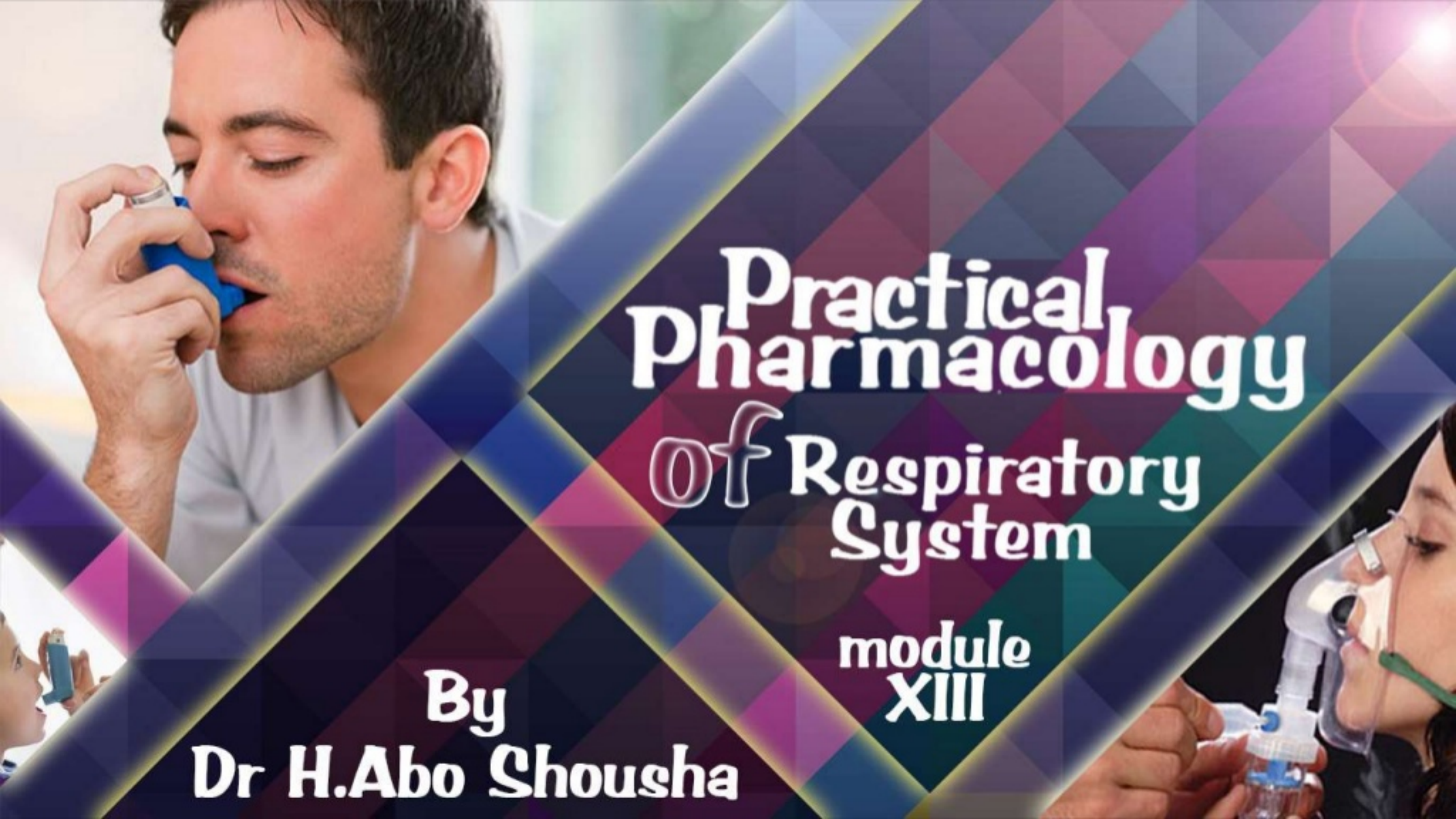




Practical Pharmacology of Respiratory System

module
XIII

By
Dr H.Abo Shousha

Practical Aspects of Asthma Drug Therapy and Methods of Administration

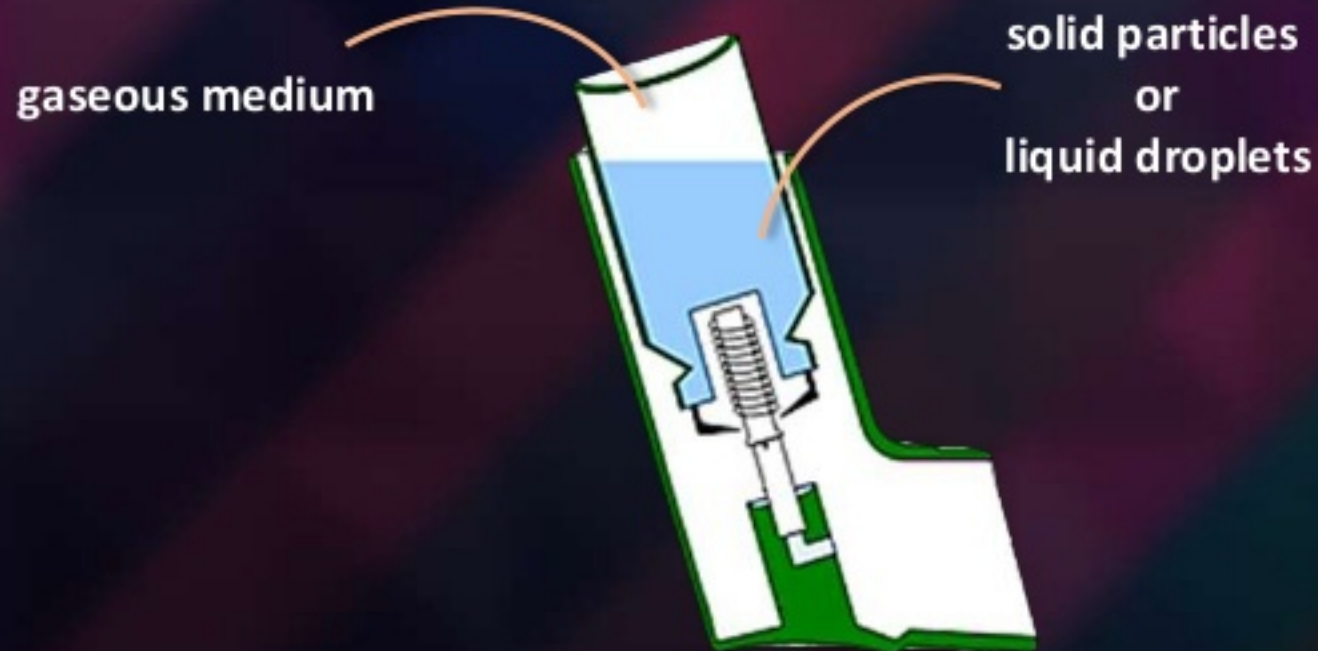
DRUG USED IN MANAGEMENT OF BRONCHIAL ASTHMA

Drug class	β_2 agonist		Anti-muscarinic	Methyl Xanthine		Corticosteroids		Leukotrienes modifiers	Mast cell stabilizers	omalizumab
Members	SABA Salbutamol Terbutaline	LABA Formoterol salmeterol	Ipratropium Tiotropium	Theophylline SR	Aminophylline	-Hydrocortisone -Prednisolone -CH ₃ prednisolone -Dexamethasone	-Beclomethasone -Fluticasone -Budesonide -Ciclesonide	Zileuton (X) montelukast, zafirlukast	Cromolyn sodium Nedocromil	
Route of administration	Inhalation Oral IV	Inhalation	Inhalation	Oral	IVI	Systemic oral IV	Inhalation	oral	Inhalation	SC
Mechanism of action	Stimulates β_2 receptors → +Adenylyl cyclase enzyme→ ↑cAMP→ relaxation		Block M ₃ receptors→ bronchodilataion & ↓secretions	-Blocks A ₁ receptors -Inhibits PDE 3,4		-Anti-inflammatory -Immunosuppressant -Up-regulation of β_2 receptors		-LOX inhibitor -Lt receptor blocker	block of chloride channels inhibiting mast cell mediator release	monoclonal antibody to the Fc portion of the IgE antibody
Indication in bronchial asthma	-In all steps of BA (reliever) -Exercise induce asthma		-In addition to β_2 agonist as reliever -Alone if β_2 agonist are contraindicated -In β -blocker induced asthma -In COPD	-With ICS as controller -In nocturnal asthma -In COPD -In acute severe asthma (IVI)		-severe persistent asthma not controlled by other drugs -severe asthma exacerbations	As long term controller alone or in combination with other drugs	1.Alternative to low-dose ICS in mild asthma 2.In addition treatment to ICS in moderate to severe asthma 3.in aspirin induced asthma 4.Allergic rhinitis.	-Prophylaxis in BA -Allergic rhinitis -Allergic conjunctiviti s	1.Severe persistent asthma that is not controlled with the combination of high-dose ICS and LABA. 2.Allergic rhinitis and chronic urticaria.
Adverse effects	1.Tremors 2.Tachycardia, arrhythmia & MI 3.Tolerance, Tachyphylaxis 4.Headache 5.Hypokalemia		1.Dry eye, dry mouth, dry skin 2.Constipation 3.Urine retention	<u>Narrow therapeutic index</u> 1.Anorexia, nausea, vomiting 2.Insomnia, headache, convulsion 3.Hypotension, arrhythmia, cardiac arrest		1.Dermal thinning 2.Impair growth 3.Osteoporosis. 4.Adrenal suppression 5.Hypertension 6.Hyperglycemia 7.Hypokalemia 8.Myopathy 9. ↓wound healing	1.hoarseness of voice 2.oro-pharyngeal candidiasis 3.small risk of cataract & glaucoma		Irritation of airway	1.Urticaria and anaphylactic reactions. 2.Injection-site pain 3.↑risk of malignancies

ADMINISTRATION OF AEROSOLIZED & INSTILLED MEDICATIONS

What is aerosol ?

An aerosol is a dispersion or suspension of solid particles or liquid droplets in a gaseous medium (e.g., air, oxygen, heliox).



AEROSOL MEDICATIONS IN RESPIRATORY DISEASES

- ADVANTAGES:

1. Noninvasive and painless.
2. Delivers drugs directly to the airways.
3. Allows delivery of high drug concentrations to the airway.
4. Inhaled β_2 -agonist bronchodilators produce a more rapid onset of action than with oral delivery.
5. Decrease systemic adverse drug reactions

AEROSOL MEDICATIONS IN RESPIRATORY DISEASES

Disadvantages:

1. Less-than-optimal **technique** decreases drug delivery and efficacy.
2. **More time** is required for drug administration.
3. Inability to determine amount of drug deposited in lungs
 - 10% deposited in bronchial tree
 - 90% Rain out→
 - Exhaled
 - Swallowed
 - Deposited orally
4. MDI may be difficult to actuate by some patients (i.e. operate)

FACTORS AFFECTING DRUG DEPOSITION

I. Optimal breathing pattern

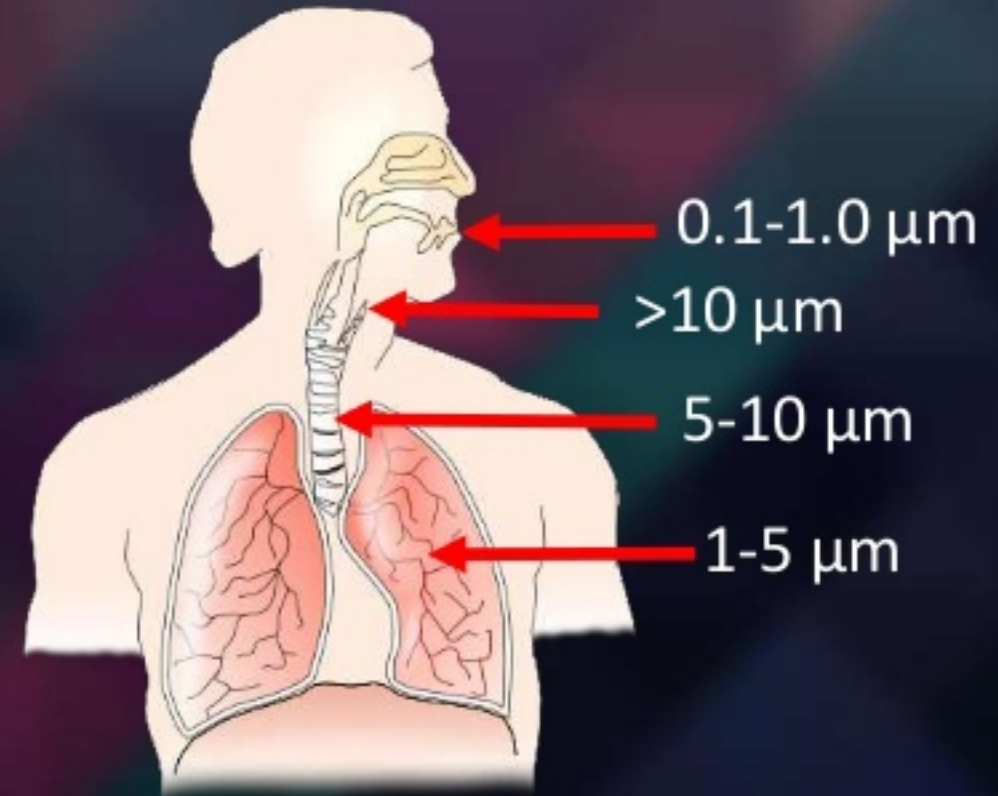
1. Slow deep inspiration then
2. End- inspiratory pause

II. Particle diameter

- The site of drug deposition depends on particle size

❖ Particle diameter:

- $>10\ \mu\text{m}$ → deposition in nasopharynx
- $5\text{-}10\ \mu\text{m}$ → Deposited in conducting airway surfaces
- $1\text{-}5\ \mu\text{m}$ → Maximum bronchiolar deposition
- $0.1\text{ to }1.0\ \mu\text{m}$ remain suspended and exhaled



AEROSOL DEVICES FOR DRUG DELIVERY

- Metered dose inhalers (MDI)
- Dry powder inhalers (DPI)
- Nebulizers

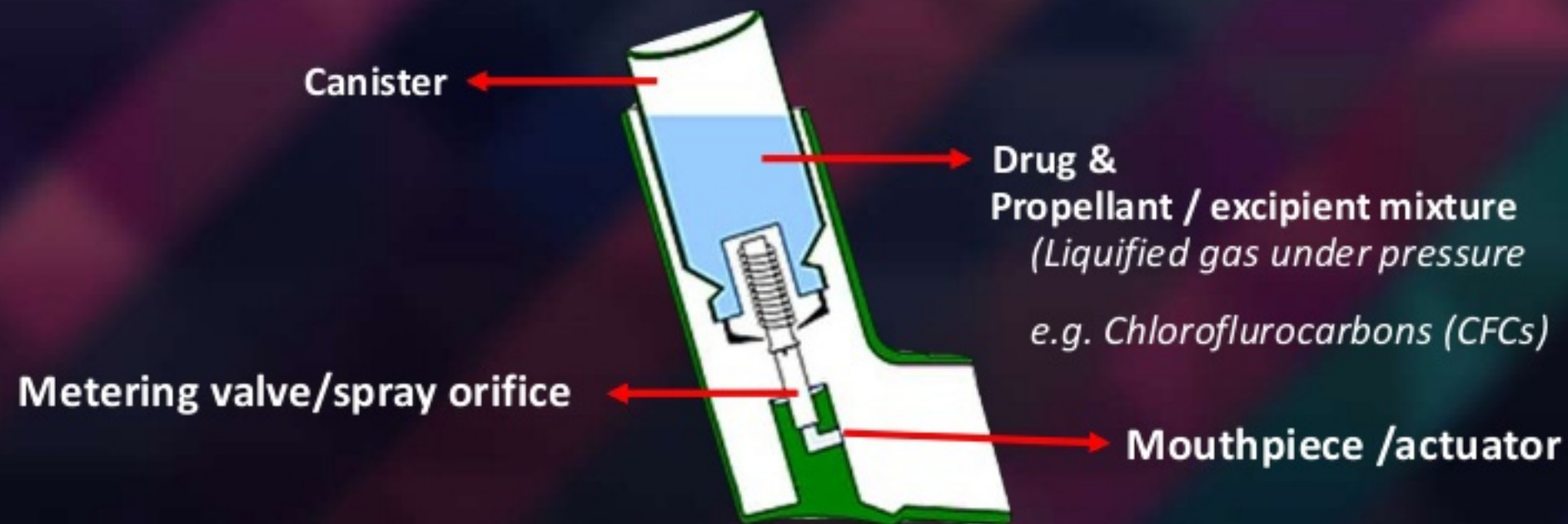
METERED DOSE INHALERS (MDIS)

❖ MDI requires

1. Patient cooperation.
2. Proper instruction and supervision by practitioner.

METERED DOSE INHALERS (MDIS)

Five major components in MDI



METERED DOSE INHALERS (MDIS)

MDI Technique



Shake



Exhale



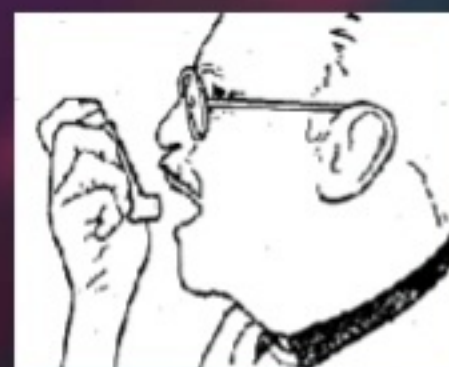
Squeeze MDI



Slow deep inspiration



Hold 5 sec at end-inspiration



Exhale



Wait 1 min



Repeat

METERED DOSE INHALERS (MDIS)

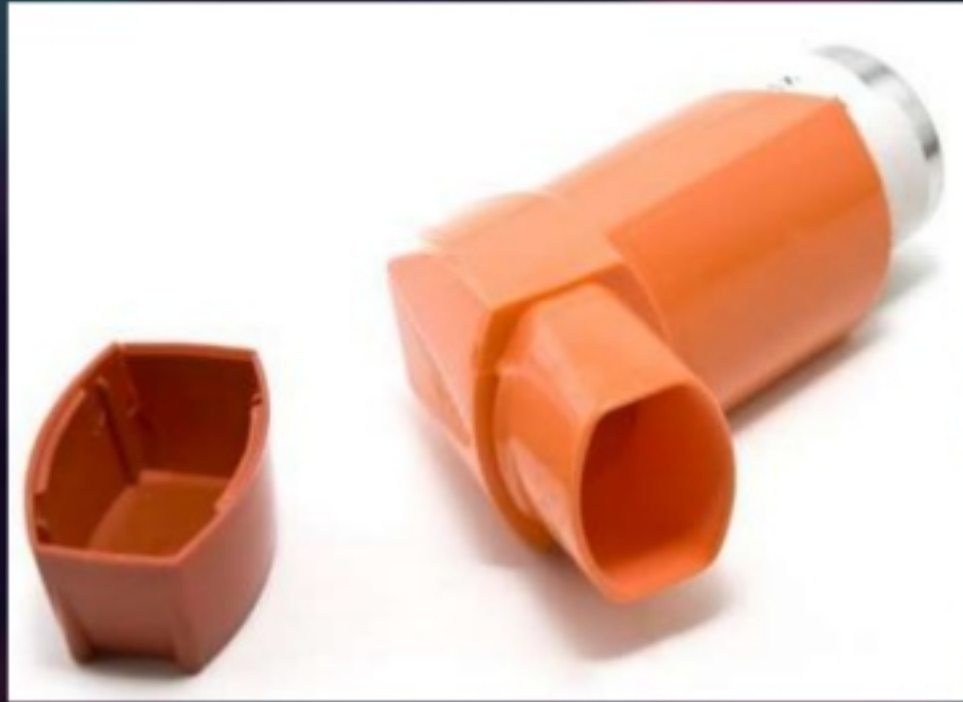
Advantages	Disadvantages
▪ MDIs are portable ▪ Treatment time is short	▪ They require hand /face breathing co-ordination ▪ CFCs are released into environment with potential for damage to protective ozone layer in the earth's atmosphere

The use of hydro-fluro-alkanes is

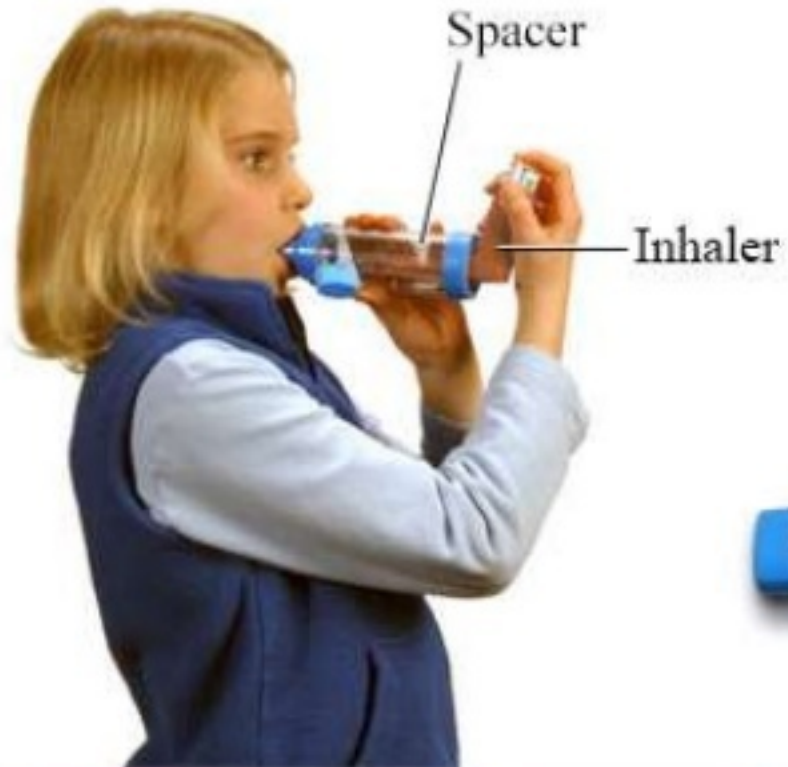
1. Environment friendly

2. No cold Freon effect to cause bronchospasm or inhibit full inspiration

METERED DOSE INHALERS (MDIS)



AEROCHAMBER (SPACER DEVICE)



© Healthwise, Inc.



AEROCHAMBER (SPACER DEVICE)

Advantage

1. Simplify coordination required for good use of MDI.
2. Reduce oro-pharyngeal drug deposition.

With inhaled corticosteroids decrease oro-pharyngeal deposition so:

- Decrease opportunistic throat infection.
- Decrease dysphonia.
- Limit swallowed drug amount.

Dry powder inhalers (DPI)



Turbohaler



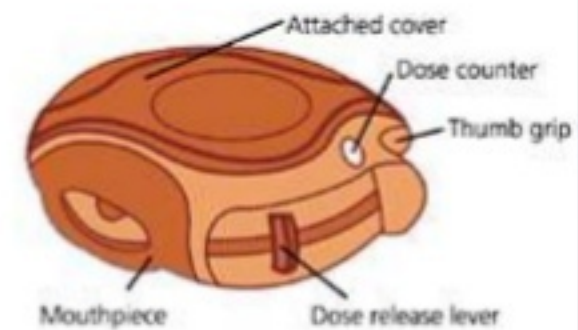
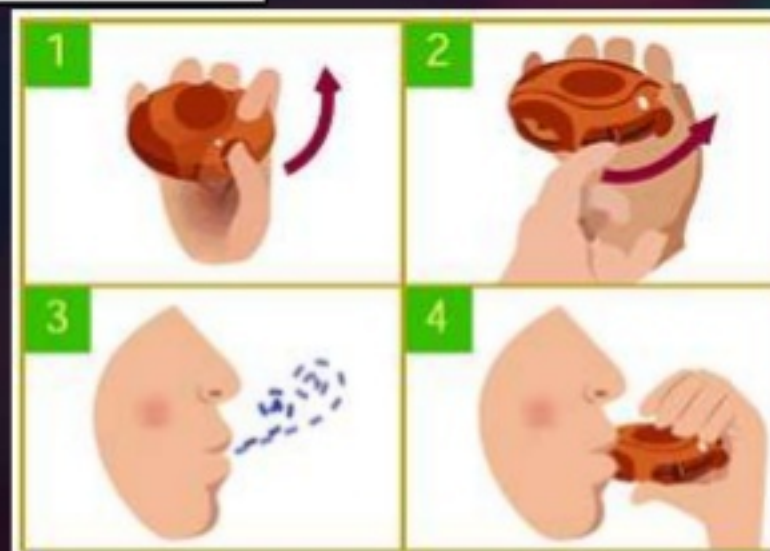
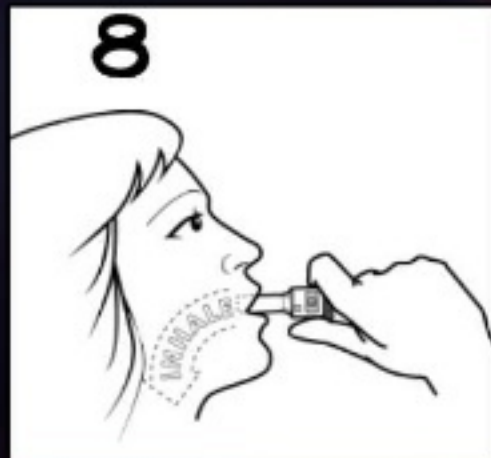
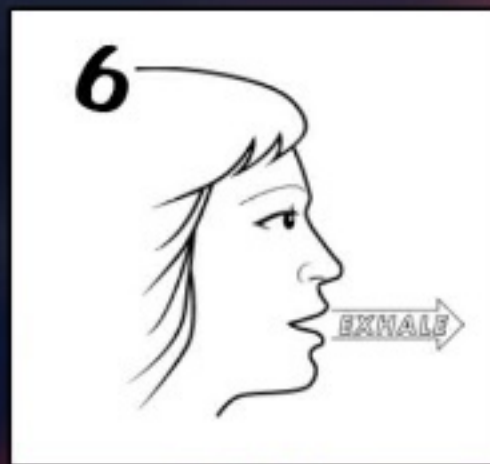
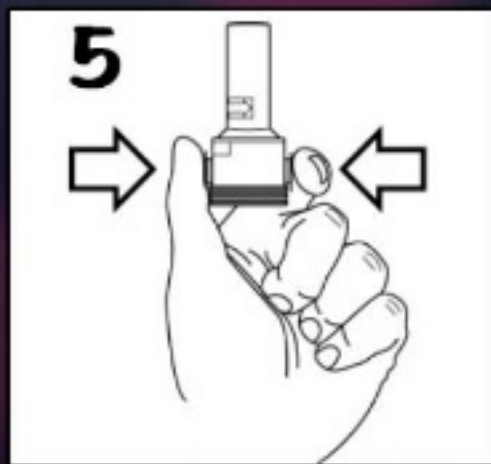
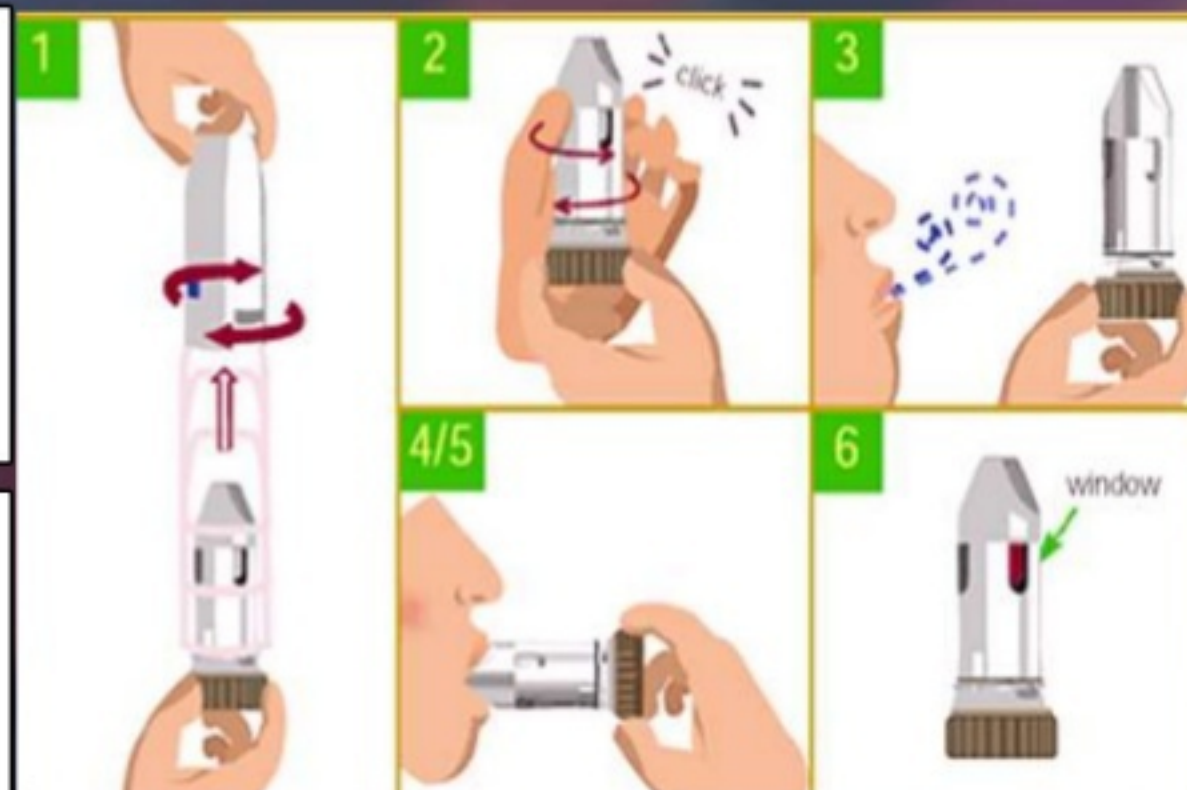
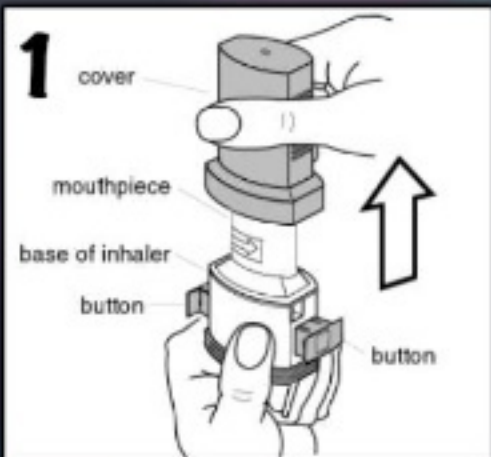
Diskus



Aerolizer

Dry powder inhalers (DPI)

Advantages	Disadvantages
1. Breath-actuated: remove the need for co-ordinate inhalation and actuation of the inhaler 2. Count of remaining drug doses is simple 3. No CFCs propellant gas	1. A high airflow is required to disperse the powder. 2. Dry powder may be irritant to the airways.



NEBULIZERS



NEBULIZERS

Advantages	Disadvantages
▪ Ability to aerosolize drug <u>mixture</u>(>1 drug) ▪ Useful in very <u>young</u> & very <u>old</u> patients or patient in acute severe asthma exacerbations who can not slow breathing & inspiratory pause is not obtainable	▪ Equipment required for use is expensive ▪ Treatment times are lengthy (Treatment time 10 minutes) ▪ Contamination is possible with inadequate cleaning



DRUG SAMPLES

❖ Identify the device

Metered dose inhaler MDI

❖ Mention drug classes

Ipratropium → antimuscarinic

Salbutamol → β_2 agonist

❖ Mention drug indications

Acute asthma symptoms and exacerbations

They are Quick-relief medications.

They have additive effects.

❖ Mention drug adverse reactions



❖ Mention drug classes

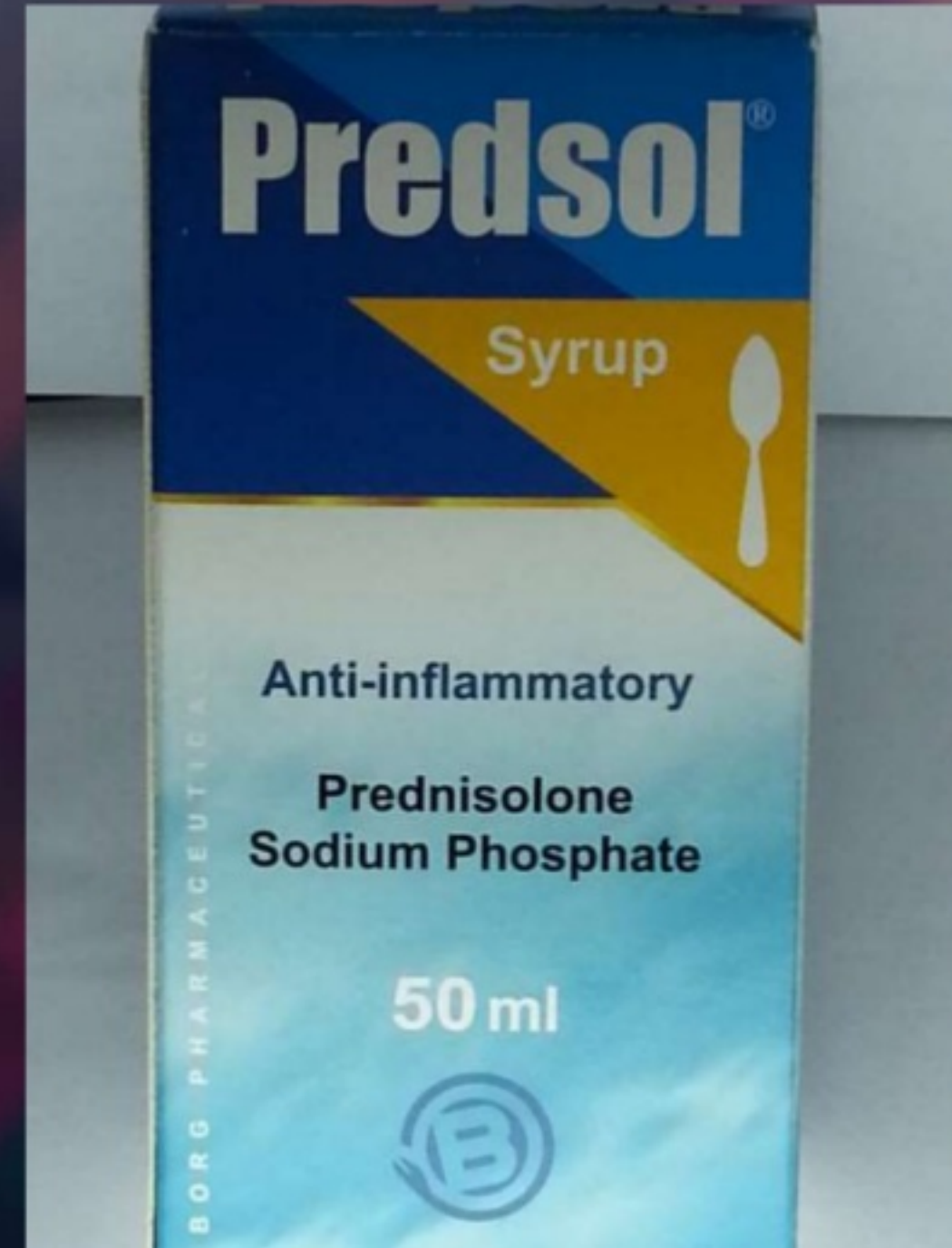
Prednisolone → systemic (oral) corticosteroids

❖ Mention drug indications

- severe persistent asthma not controlled by other drugs
- severe asthma exacerbations

❖ Mention drug adverse reactions

- | | |
|-------------------|-----------------------|
| 1.Dermal thinning | 2.Impair growth |
| 3.Osteoporosis. | 4.Adrenal suppression |
| 5.Hypertension | 6.Hyperglycemia |
| 7.Hypokalemia | 8.Myopathy |
| 9.↓wound healing | |



❖ Mention drug classes

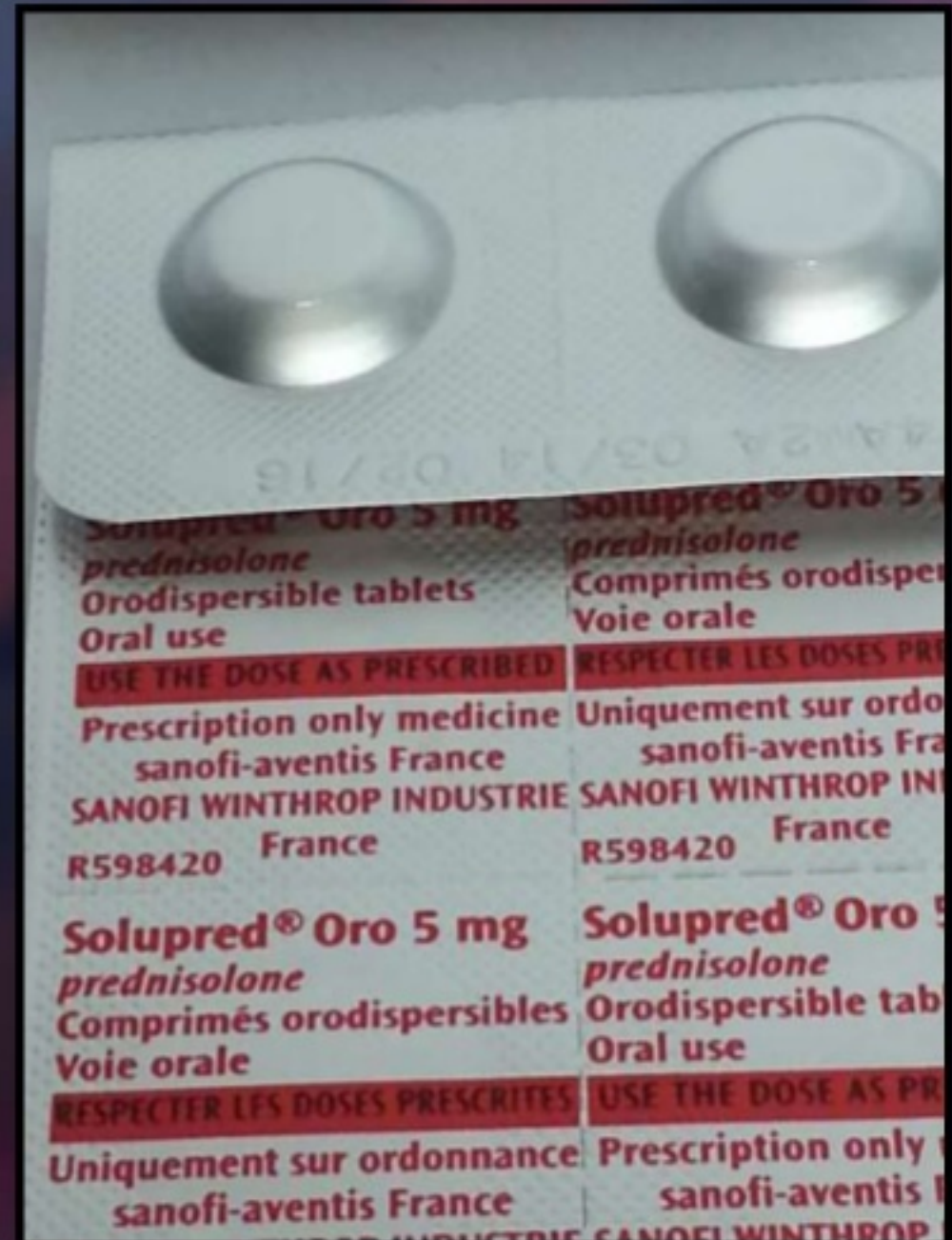
Prednisolone → systemic (oral) corticosteroids

❖ Mention drug indications

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❖ Mention drug adverse reactions

- | | |
|-------------------|-----------------------|
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| 5.Hypertension | 6.Hyperglycemia |
| 7.Hypokalemia | 8.Myopathy |
| 9.↓ wound healing | |



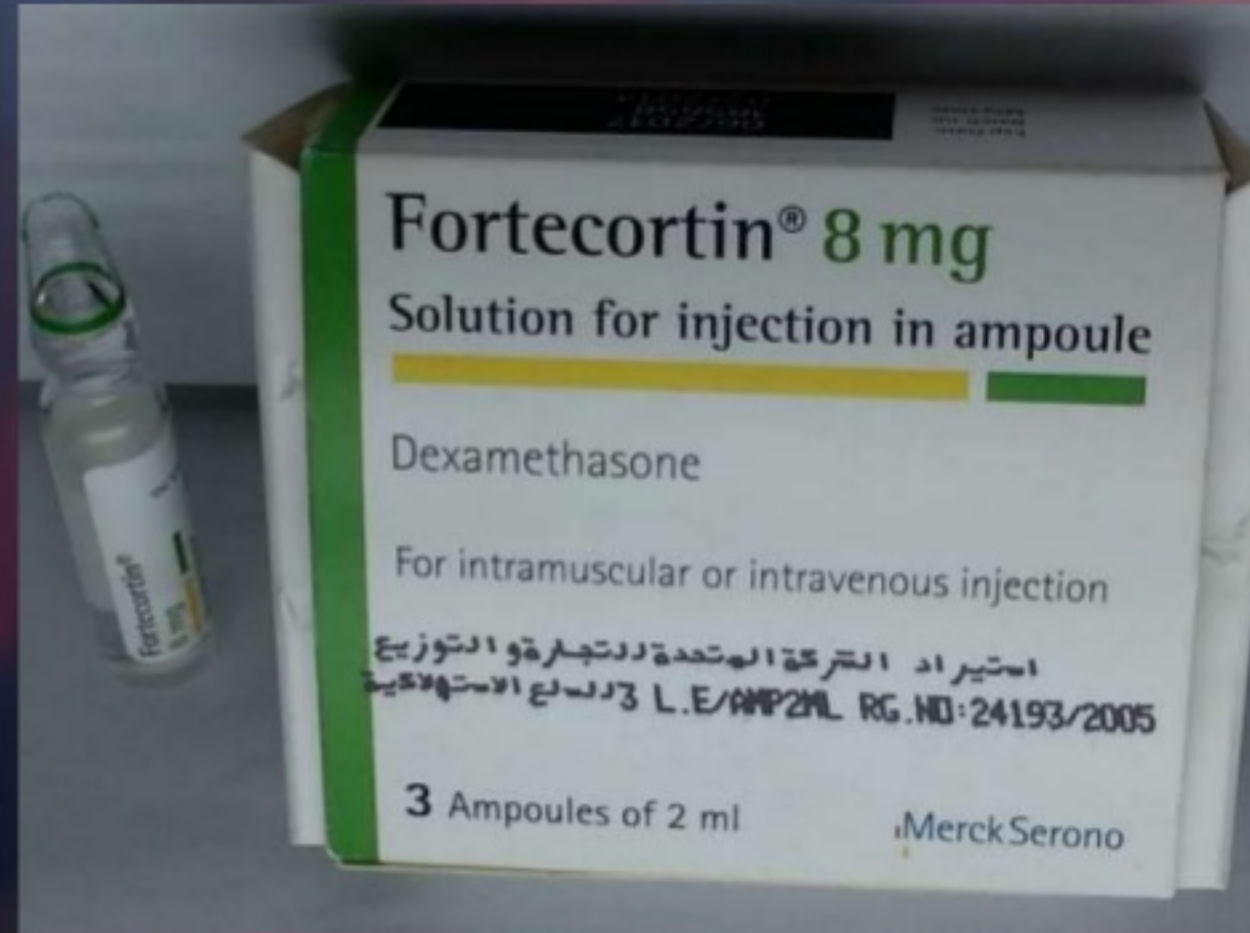
❖ Mention drug classes

Dexamethasone → systemic (injection)
corticosteroids

Long acting Synthetic corticosteroid.

❖ Mention drug indications

- severe persistent asthma not controlled by other drugs
- severe asthma exacerbations



It is a long acting Synthetic corticosteroid with a half-life approximately double that Of prednisolone (54 hours) and a more potent anti-inflammatory effect.

A 2-dose regimen of dexamethasone is as effective as a 5-day course of prednisolone.

❖ Mention drug classes

(SR) oral Theophylline → Methyl Xanthine.

❖ Mention drug indications

Long-term control of:

1. Mild to moderate asthma (as add-on therapy to ICs)
2. Nocturnal asthma.
3. Some cases of COPD.

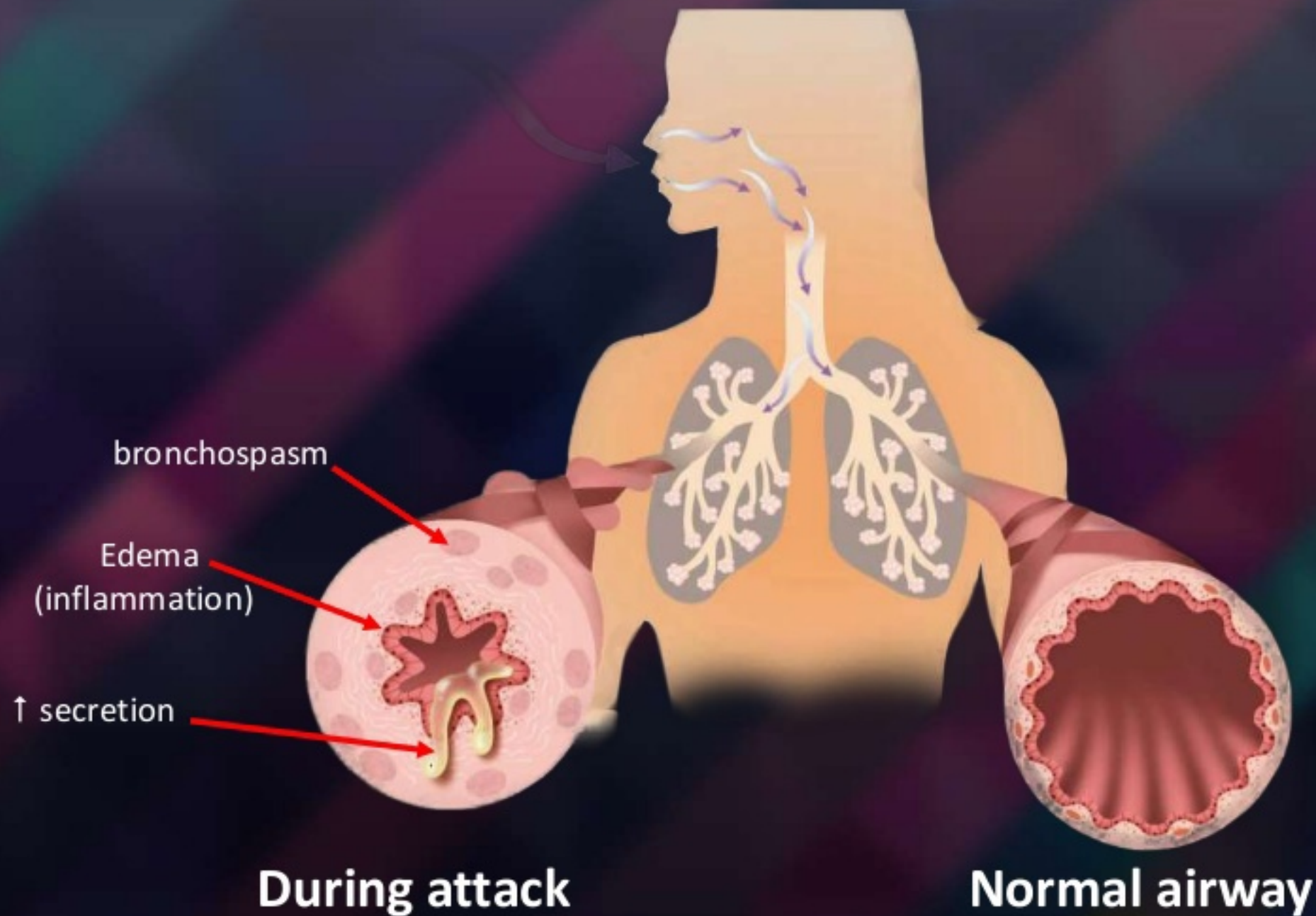
❖ Mention drug adverse reactions

Narrow therapeutic index

1. Anorexia, nausea, vomiting
2. Insomnia, headache, convulsion
3. Hypotension, arrhythmia, cardiac arrest



PATHOLOGY OF BRONCHIAL ASTHMA



Treatment of bronchial asthma

Short term reliever	Long term controller
- SABA - Antimuscarinic - Methyl xanthine - Mg sulphate	- Corticosteroids (inhaled , systemic) - LABA - Methyl xanthine SR - Leukotrienes modifiers - Mast cell stabilizer - omalizumab

GINA classification of BA

		Day symptoms	Night symptoms	FEV ₁ or PEF	reliever	controller
Step 1	Intermittent	< 1 / week	≤ 2/ month	≥ 80%	SABA + other reliever	NO
Step 2	Mild persistent	< 1/ day	> 2/ month	≥ 80%		Only One ICS or (LTs modifier or theophylline)
Step 3	Moderate persistent	Daily	>1/ week	60-80 %		Two drugs ICS + LABA or (LTs modifier or theophylline) Or ICS alone (High dose)
step4	Severe persistent	Continous	frequent	≤ 60%		Three drugs ICS + LABA + (LTs modifier or theophylline) + systemic CST if not controlled +omalizumab

Mechanism of action & receptors



STUDY OF THE EFFECT OF BRONCHOCONSTRICTOR AND BRONCHODILATOR AGENTS IN THE LABORATORY

Use of isolated guinea pig trachealis muscle is a
convenient and useful way



METHODS

- A Guinea pig was killed by cervical dislocation.
- The trachea was rapidly removed and placed in petri-dish containing oxygenated **modified Krebs-Henseleit** solution
(NaCl, KCl, MgSO₄, CaCl₂, NaHCO₃, Glucose).
- The trachea was then cut horizontally into transverse pieces. Six pieces were tied together to form a tracheal chain.
- Tracheal chain was suspended in **20-ml organ bath** containing Krebs-Henseleit solution **(pH 7.4)** bubbled with **carbogen (95% O₂ and 5% CO₂)** and kept at **37 °C**.

METHODS

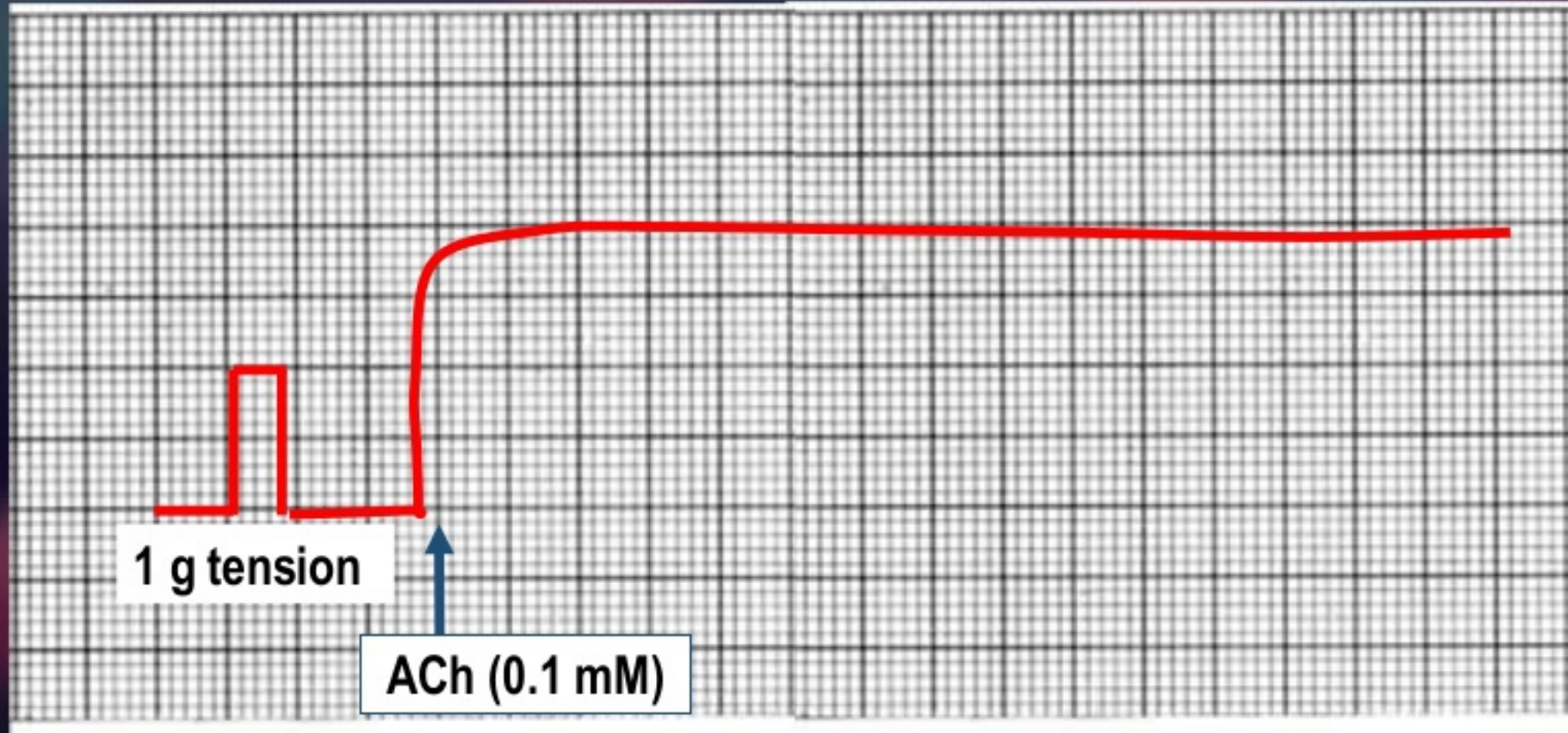
- Tissues were allowed to equilibrate for one hour with frequent washing under resting tension of 1 g which was found to be optimal for measuring changes in tension.
- Isometric contractile responses were measured with force-displacement transducers and recorded on a polygraph recorder.



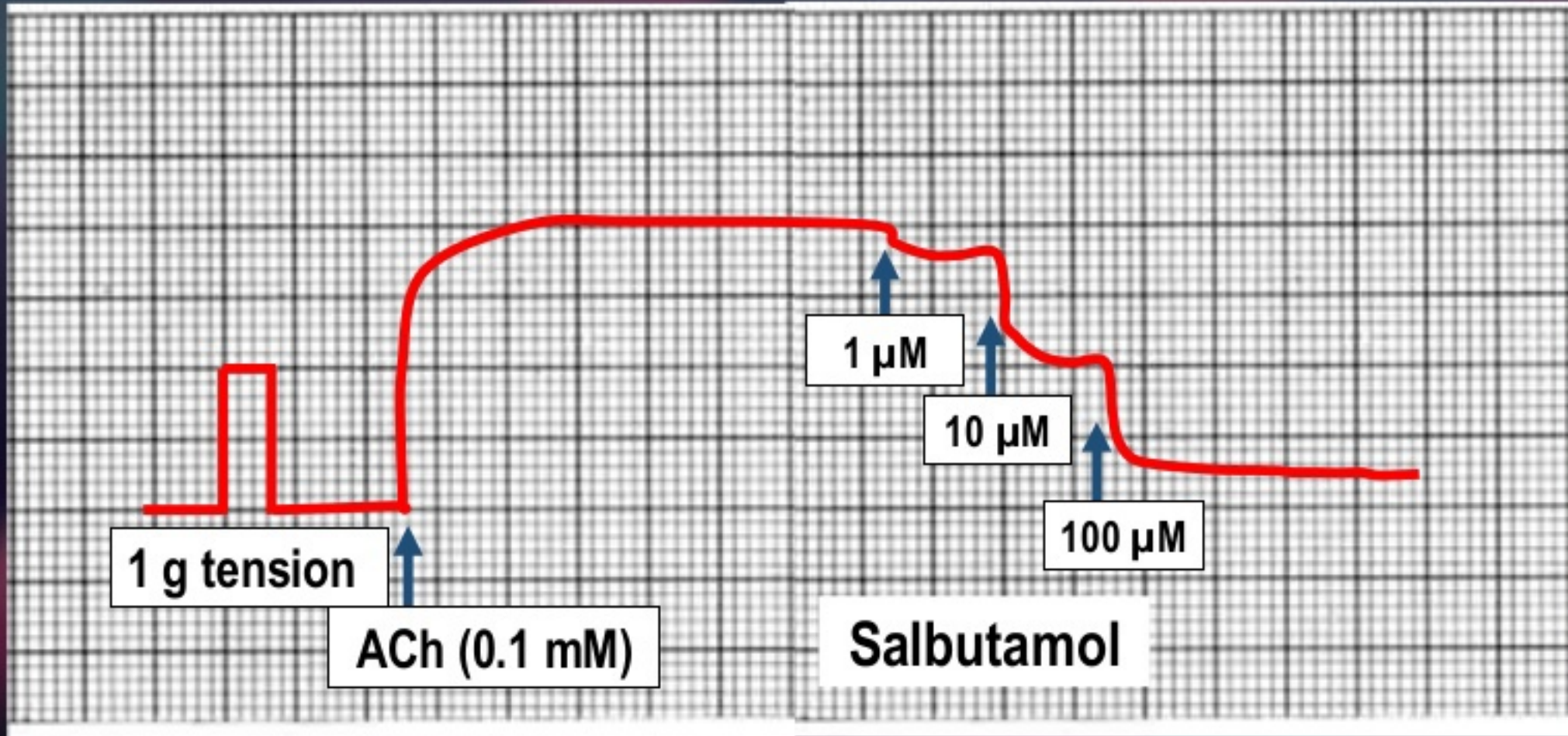
PROCEDURE

I. Effect of broncho-constrictor agents (acetyl choline, histamine and KCl) on guinea pig trachealis muscle:

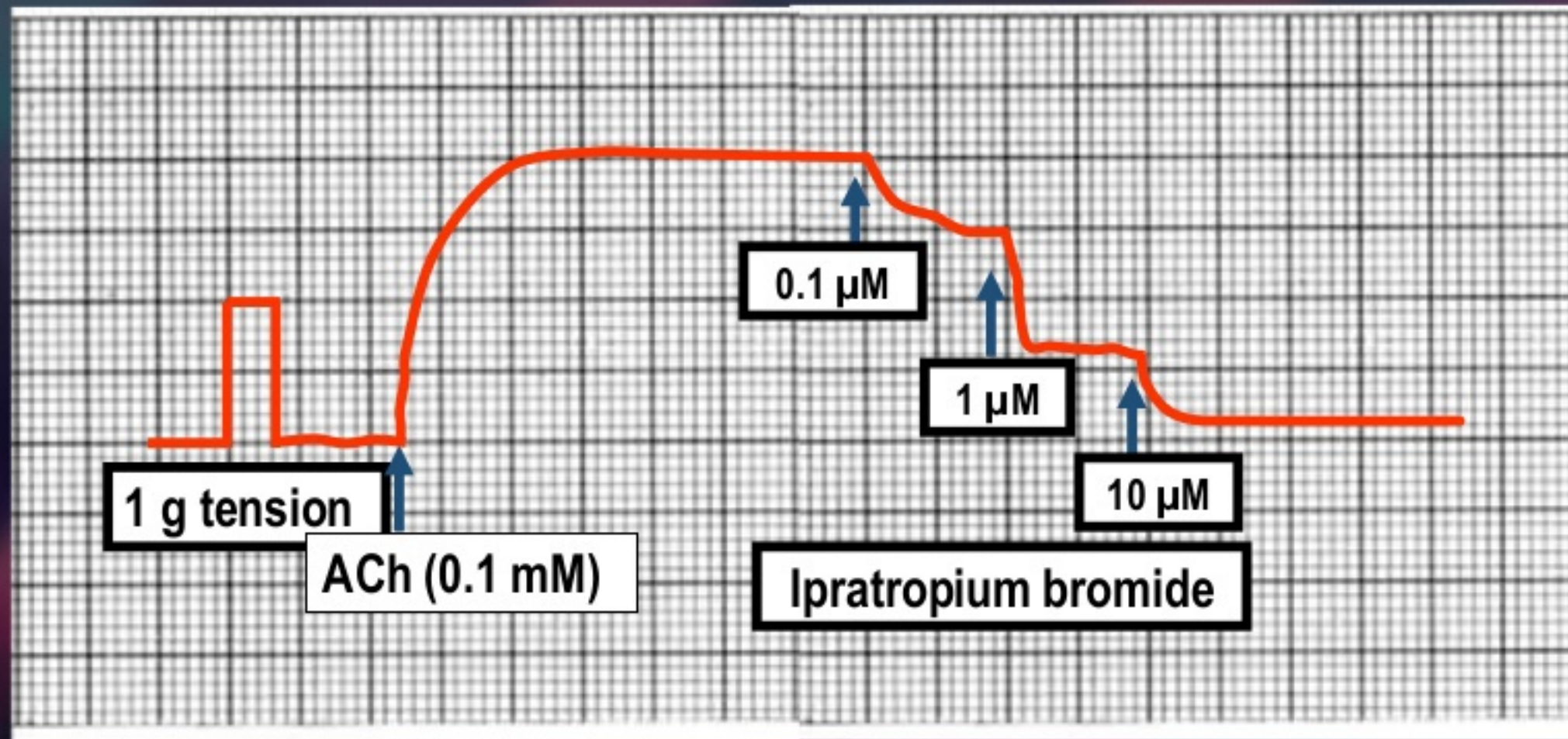
- At the end of the equilibration period, a base line was recorded for 10 min.
- A submaximal dose of ACh, histamine and KCl was chosen.
- The increase in muscle tone (muscle contraction) was induced by either ACh (0.1 mM), histamine (20 μ M), or KCl (30 mM) . The induced tone was then traced for 10 min which was sufficient to reach a plateau.



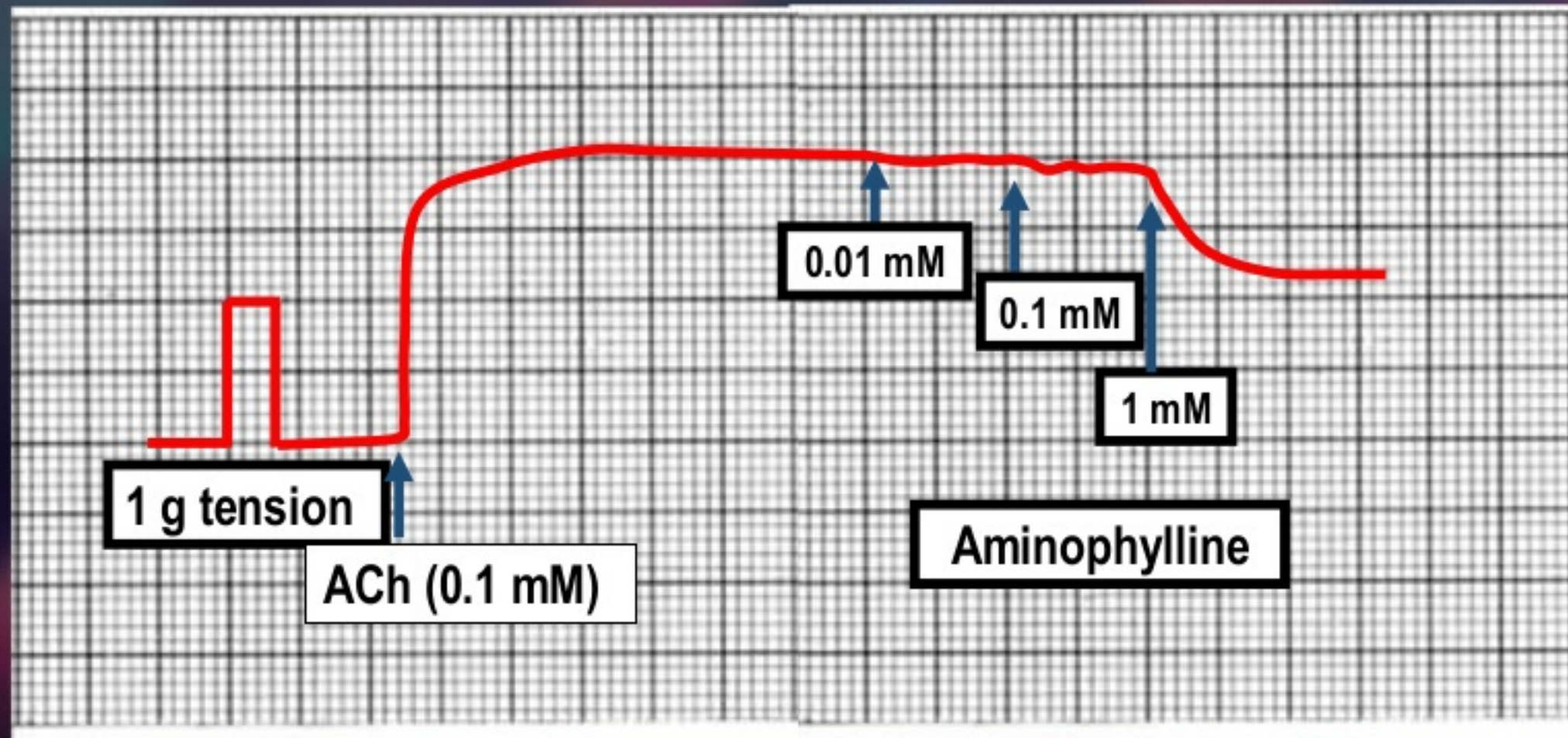
Effect of ACh (0.1 mM) on guinea pig trachealis muscle.



Effect of salbutamol (1-100 μM) on ACh-induced guinea pig trachealis muscle contractions.



Effect of ipratropium bromide(0.1-10 μM) on ACh-induced guinea pig trachealis muscle contractions.



Effect of aminophylline (0.01-1 μ M) on ACh-induced guinea pig trachealis muscle contractions.

- The relaxant effect of each drug was evaluated by measuring the **height of muscle contraction** induced by Ach on the curve in comparison with this height after addition of each dose of the relaxant drugs.
- Calculate the **% relaxation** with each concentration of the drugs used.

$$\% \text{ relaxation} = 100 - \frac{\text{height of muscle contraction after relaxant drug (cm)}}{\text{height of muscle contraction before relaxant drug (cm)}} \times 100$$

$$\% \text{ relaxation} = \frac{\text{height of contraction after Ach} - \text{height of relaxation}}{\text{height of contraction after Ach}} \times 100$$

Drugs	Concentrations added	Measurements in cm	% relaxation
Salbutamol	Before	4	0
	After	3	25
	After	2	50
	After	0.5	87.5
Ipratropium bromide	Before	4	0
	After	3	25
	After	1	75
	After	0.1	97.5
Aminophylline	Before	4	0
	After	4	0
	After	3.8	5
	After	2.2	45

A 5 year old boy comes with respiratory distress to pediatric clinic. His parents said that he has daily night coughing for 2 weeks , morning sneezing, nasal stuffing and mild fever. Parents believe that his episode of common cold was the trigger for these symptoms.

History:

He has similar attacks in the past, but this episode is worse, his history is notable for eczema and dry skin since infancy. His family history is notable for a brother who has asthma. In his home environment, there are no smokers or pets.

Signs:

Vital signs: temp. 38.1, pulse 100, resp. rate 24, blood pressure 85/65, oxygen sat. 99% in room air.

He is alert, nasal mucosa is wet with clear discharge.

His chest is hyper resonant to percussion and wheezes are heard on auscultation.

Q1. prescribe an initial therapy for acute asthma exacerbation of moderate severity

Patient's name:
Patient's address:

Doctor's name:
Doctor's address:

Date:

Diagnosis: **Moderate acute asthma**
R/ **exacerbation**

- **Salbutamol solution by nebulizer 2.5 mg/ 20 min (3 doses in 1h)**
- **Prednisolone syrup 2 mg/kg/day**

Doctor Signature

Patient's name:
Patient's address:

Doctor's name:
Doctor's address:

Date:

Diagnosis: Moderate acute asthma

R/ exacerbation

- Salbutamol solution by nebulizer 2.5 mg/ 20 min (3 doses in 1h)

+

- Ipratropium solution by nebulizer 2.5 mg/ 20 min(3 doses in 1h)

- Prednisolone syrup 2 mg/kg/day

Doctor Signature

Q2. prescribe a long term maintenance therapy for the child moderate persistent asthma

Patient's name:

Doctor's name:

Patient's address:

Doctor's address:

Date:

Diagnosis: **moderate persistent asthma**

R/

Doctor Signature

GINA classification of BA

		Day symptoms	Night symptoms	FEV ₁ or PEF	reliever	controller
Step 1	Intermittent	< 1 / week	≤ 2/ month	≥ 80%	SABA ± other reliever	NO
Step 2	Mild persistent	< 1/ day	> 2/ month	≥ 80%		Only One <u>ICS</u> or (LTs modifier or theophylline)
Step 3	Moderate persistent	Daily	>1/ week	60-80 %		Two drugs <u>ICS</u> + <u>LABA</u> <u>or</u> (LTs modifier or theophylline) <u>Or</u> ICS alone (High dose)
step4	Severe persistent	Continous	frequent	≤ 60%		Three drugs <u>ICS</u> + <u>LABA</u> + (LTs modifier or theophylline) + systemic CST if not controlled +omalizumab

Q2. prescribe a long term maintenance therapy for the child moderate persistent asthma

Patient's name:

Doctor's name:

Patient's address:

Doctor's address:

Date:

Diagnosis: **moderate persistent asthma**

R/

Beclomethasone MDI 150 mcg / dose

Two puffs twice daily

Doctor Signature

- I-Complete:

1-----**Ach**----- causes bronchoconstriction by acting on**M₃**..... receptors.

2-----**Histamine**----- acts on H1 receptors producing bronchospasm, while -----**Kcl**----- acts nonspecifically to constrict bronchial muscles.

3-----**B₂ adrenergic agonists**..... and**Xanthine derivatives**..... cause bronchodilatation through increasing the intracellular level of cAMP by different mechanisms.

4-----**Ipratropium**..... acts through competitive antagonism with ACh on -----**M₃**----- receptors of bronchial smooth muscles and is taken by**inhalation**.....

5- The relaxant effect of each drug is evaluated by measuring the percent change in the **height** of muscle contraction induced by **Ach** on the curve after addition of each dose of the relaxant drugs.

6- The tracheal chain is suspended in 20-ml organ bath containing
Krebs-Henseleit solution..... solution.

7- Isometric contractile responses are measured with
force-displacement transducers.....and recorded on a **polygraph recorder**.....

8-During testing the effect of bronchodilator agents on contractions induced by bronchoconstrictors , a**submaximal**.....dose of these bronchoconstrictors is chosen.

9-After adding ACh on trachealis muscle, the induced tone is traced for a period of**10 minutes**.....which is sufficient to reach a plateau.

• **IV-Put true or false:**

- 1- Salbutamol acts on sympathetic β_1 receptors to relax bronchial smooth muscles
· **False**
- 2-Ipratropium bromide is a muscarinic agonist that relaxes bronchial smooth muscles . **False**
- 3-Aminophylline increases intracellular cAMP by inhibition of phospho-diesterase enzyme . **True**
- 4-The guinea pig tracheal chain is bubbled with carbogen and kept at 37 °C in the organ bath .**True**
- 5- ACh is a parasympathetic agonist that acts on M_2 receptors in bronchial muscles to induce contractions . **False**

THANK YOU

